Review Article

A Review on Atorvastatin Co Administration with Ezetimibe for the Treatment of Hypercholesterolemia

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ABSTRACT

Therapeutic success of any therapy depends on the patient's compliance towards the therapy. Tablets are the most popular dosage form because of its unique properties such as ease of administration, low cost and non-invasive therapy etc. The present study aims to develop and evaluate to provide polytherapy through a single immediate release tablet in which combination of Atorvastatin and ezitimibe were used for treatment of hyperlipidemias.

Although widely used in lipid lowering therapy, atrovastatin, a HMG CoA reductase inhibitor (even when administered at high doses) is frequently insufficient to achieve guideline-recommended LDL-C goals for many patients with hypercholesterolemia in everyday clinical practice. As a consequence, a wide therapeutic gap exists between target LDL-C levels and those typically achieved in clinical practice. A recent and more effective strategy used for treating for hyperlipidemias , by co-administering ezetimibe, a novel agent inhibiting cholesterol absorption, with a atrovastatin, which inhibits cholesterol biosynthesis in the liver.

We summarize that Ezetimibe with the recommended dosage of 10mg daily can be effectively and safely co-administered with any dose of any statin and, compared with the single inhibition of cholesterol production, afforded by statins alone, provides consistently greater reductions in LDL-C through dual inhibition of both cholesterol production and absorption.

Keywords: Ezetimibe, Atrovastatin, hypercholesterolemia, cholesterol absorption, HMG COA Reductase inhibitors, LDL-C.

INTRODUCTION

Over the past two decades, the primary prevention and treatment (secondary prevention) of coronary artery disease (CAD) has been dramatically altered with the advent of effective lipid-lowering agents, especially 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors,or statins. Statins are potent inhibitors of the rate-limiting enzyme involved in sterol synthesis, HMG-CoA reductase. Since their introduction in clinical practice in the mid-1980s, the use of statins has grown rapidly. Multiple clinical trials have shown the abilityof statins to markedly reduce serum levels of TC, LDL-C, triglycerides (TGs) and apolipoprotein B (Apo B). This effect on serum lipids and lipoprotein lipids has dramatically changed the relative risk of cardiovascular morbidity and mortality and on total mortality (6,10-13). The effect of statins on high-density lipoprotein cholesterol (HDL-C) is usually modest (5% to 10% increase).

According to a recent study, a large proportion of high-risk hyperlipidemic patients receiving statins alone are not at goal even when physicians were free to use any statin and titrate according to their professional judgment . Over half (52%) of patients did not achieve LDL-C goal on the initial dose of statin, and 86% of these patients had still not reached goal after 6 months . Thus, a wide therapeutic gap exists between target LDL-C levels and what is achieved in clinical practice. The therapeutic gap will undoubtedly increase in light of the recent amendments of the National Cholesterol Education Program Adult Treatment Program III (NCEP Vascular Health and Risk Management 2008:4(2) Grigore et al ATP III) guidelines, which recommend even more aggressive reductions in LDL-C levels for patients at high risk of CHD . The more aggressive

cholesterol treatment goals proposed by the revised guidelines call for a more effective approach to maximize the cardiovascular benefits associated with lower LDL-C levels.

In the human body there are two major sources of cholesterol: first, the gastrointestinal tract where daily cholesterol is derived from the diet, bile input and desquamated cells ; second, the liver which is the major source of cholesterol synthesis; in the human body . Approximately 50% of the cholesterol pool is absorbed and recirculated through the intestine, while the remainder is excreted through the feces . The intestinal pool is composed of both dietary, and the majority, from biliary excretion. A recent and more effective therapeutic strategy, is to treat both sources of cholesterol simultaneously with a complementary mechanism of action, by co-administering ezetimibe, a novel agent inhibiting cholesterol absorption, together with a statin, which inhibits cholesterol production in the liver . This results in dual inhibition of both sources of cholesterol provides significantly greater LDL-C reduction and subsequent goal attainment.

Ezetimibe can be effectively co-administered with any dose of any statin; indeed the benefi ts are consistent across the statin brand and dose subgroups and compared with single inhibition of cholesterol production, afforded by statins alone,

provides consistently greater reductions in LDL-C through dual inhibition of both cholesterol production and absorption The single product of ezetimibe/ simvastatin provides superior LDL-C lowering effi cacy with improved LDL-C goal attainment .

Here we summarize the pivotal role of both the liver and intestine in the overall balance of cholesterol in the body and describe the clinical impact and relevance of inhibiting both sources of cholesterol.

Pathophysiology of Hyperlipidemias

An understanding of the biology of the lipoproteins and the pathophysiology of hyperlipidemic states is essential to the rational choice of treatment regimen.

1. **Exogenous pathway**

Route of uptake of dietary lipids Chylomicrons (CM) are complexes of triglycerides (TG), cholesteryl esters (CE), and apoproteins. After the removal of triglycerides they become chylomicron remnants. Chylomicrons are degraded by lipoprotein lipase on endothelial cells of adipose tissue and muscle. After removal of TG for storage, the CM remnants are transported to the liver. This results in dietary TG stored in adipose tissue and muscles.

2. **Endogenous pathway**

Route for distribution of cholesteryl esters (CE) from liver to target cells VLDL is secreted by the liver into plasma and transported to adipose tissue and muscles, where lipoprotein lipase extracts most triglycerides. The remnant IDL is either taken up by the liver or circulated until the remaining triglycerides are removed forming LDL particles,rich in cholesterol. LDL is cleared from plasma through LDL receptor-mediated endocytosis. This results in transfer of TG from liver to target cells via VLDL, as well as, transfer of CE from liver to target cells via LDL.

3. **Route for cholesterol recovery**

Reverse cholesterol transport is a pathway where cholesterol is transported from atherosclerotic plaques or other lipids back to liver to be excreted into the faecus via bile. As cell dies and the cell membranes turnover, free cholesterol is released into the plasma. It is immediately absorbed into HDL particles, esterified with a long chain fatty acid by lecithin cholesterol acyl transferase (LCAT), and transferred to VLDL or IDL by a cholesteryl ester transfer protein in plasma. Eventually, it is taken up by the liver as IDL or LDL, thus resulting in the recovery of cholesterol from cell membranes and reincorporation into LDL pool or return to liver.

4. **De novo cholesterol biosynthesis**

Liver synthesizes 2/3rd of the total cholesterol made in the body. The rate limiting enzyme is 3-hydroxy-3-

methylglutaryl(HMG)-CoA reductase and provides feedback regulation by controlling the cholesterol concentrations in cells.

5. **Cholesterol excretion by enterohepatic circulation:**
Bile salts are synthesized from cholesterol in the liver, released into the intestine, and recycled. A small amount of bile acid is excreted. This results in conversion of liver ncholesterol to bile salts for excretion.

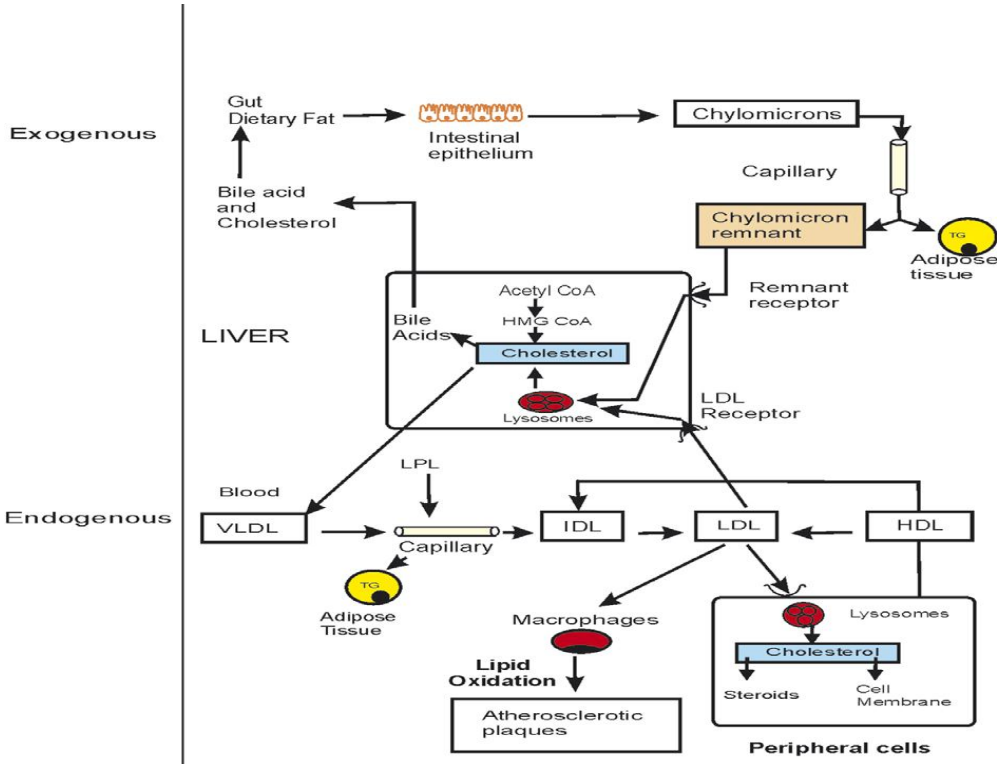

Fig. Endogenous and exogenous transport of lipids

Targets of Therapy for Hyperlipidemia
Lowering LDL-C is the primary goal of treatment of hyperlipidemia. Current guidelines from the NCEP ATP III recommend that the target LDL-C should be based on the patient's risk for developing coronary heart disease (CHD). Risk factors include age, gender, and family history of premature CHD, hypertension, current cigarette smoking, and low HDL-C levels. HDL-C levels R 60 mg/dL count as a negative risk factor and remove one risk factor from the total number. Patients who have two or more risk factors are categorized further by assessing their 10-year risk using the Framingham score. For patients who have a history of CHD or CHD equivalent such as diabetes, peripheral vascular disease, carotid artery stenosis, or abdominal aneurysm or who have a calculated 10-year risk greater than 20%, the LDL-C goal should be a level less than 100 mg/dL. In patients at very high risk, a goal of LDL-C less than 70 mg/dL is optional. If the HDL-C level is R60 mg/dL, subtract one risk factor, because high HDL-C levels decrease the risk of coronary heart disease. Data from Expert Panel on Detection, Evaluation and Treatment of High Blood Cholesterol in Adults. Executive summary of the third report of the National Cholesterol Education Program (NCEP) Expert Panel on

Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III).

Very high risk is defined as established vascular disease and any additional conditions including multiple risk factors (such as diabetes), severe and poorly controlled risk factors (eg, cigarette smoking), metabolic syndrome (high triglyceride, low HDL-C levels), and acute coronary syndromes.

The American Diabetes Association also recommends a target LDL-C level of less than 70 mg/dL in diabetic patients who have CVD.10 The NCEP guidelines recommend that for patients who have more than two risk factors but a 10-year risk % 20%, the target LDL-C level should be less than 130 mg/dL. For patients who have no or one risk factor, an LDL-C level less than160 mg/dL should be the goal.

Therapeutic lifestyle changes should be initiated whenever a person's LDL-C level is above the target based on the risk assessment. In general, drug therapy should be started in conjunction with therapeutic lifestyle changes without delay when the LDLC level is above target in high-risk or moderately high-risk groups, including patients who have CHD or CHD equivalents and those who have two or more risk factors and a 10-year risk score between10% and 20%. For the other patients at low or moderately low risk, medical treatment should be initiated together with therapeutic lifestyle changes if the LDL-C level is more than 30 mg/dL above the target. For patients who have an LDL-C level less than 30 mg/dL above the target, therapeutic lifestyle changes alone may be adequate to lower the cholesterol into the target range, obviating the need for drug therapy. The 2004 NCEP update states that drug therapy to obtain a 30% reduction in LDL-C level from baseline can be considered even when the LDL-C level is less than 30 mg/dL above the target. Once the LDL-C goal is reached, the non-HDL-C goal, which is 30 mg/dL above the LDL-C goal, and the HDL-C (> 40 mg/dL) and triglyceride (< 150 mg/dL) goals can be targeted.

STATINS

Hydroxymethyl glutarate coenzyme A (HMG-CoA) reductase inhibitors (statins) competitively inhibit HMG-coenzyme A reductase, which is involved in the rate limiting step of cholesterol biosynthesis in the liver. In addition, statins increase levels of HDL which has cardiovascular protective effects. Furthermore, statins reduce the susceptibility of lipoproteins to oxidation, both in vitro and ex vivo. Oxidative modification of LDL appears to play a key role in mediating the uptake of lipoprotein cholesterol by macrophages.

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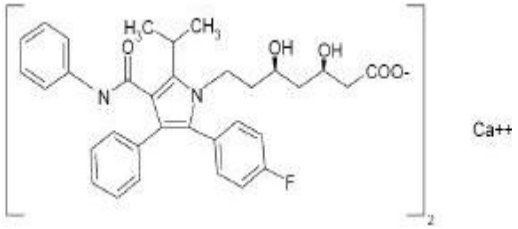


Fig: Structure of atrovastatin

HMG-CoA reductase chemistry

HMG-CoA reductase (HMGR) catalyzes the rate-limiting step incholesterol biosynthesis. The reduction of 3-hydroxy-3- methylglutaric acid (HMG) to revalonic acid involves the transfer of 4 electrons (via 2 molecules of NADPH cofactor) to a substrate that has been activated for reaction with the sulfhydryl (–SH) containing coenzyme A(designated as CoASH). The binding site for the HMG-CoA substrate is of critical importance. Some of the key amino acid residues of HMGR that bind to the HMG-CoA substrate have been identified

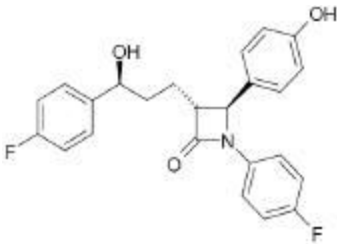
Mechanism of Action

The statins work by inhibiting HMG-CoA reductase, which catalyzes the conversion of the substrate, HMG-CoA, to mevalonate; this reaction is an early and rate-limiting step in the biosynthesis of cholesterol.19 Structurally, the statins are similar to HMG-CoA and occupy a portion of the active binding site on the enzyme, blocking access of the substrate to the binding site.20 This competitive inhibition leads to decreased production of cholesterol and thus to a decrease of intracellular cholesterol levels, causing up-regulation of LDL receptors and a

reduction in LDL-C levels because of the increased clearance by the LDL receptor. Statins also reduce the release of lipoproteins from the liver into the circulation. At high doses, statins decrease triglyceride levels through the clearance of very low-density lipoprotein (VLDL) as well as by decreasing the production of lipoproteins. 10 mg, was associated with a higher rate of premature discontinuation (7.2% versus 5.3%; P < .001)

Ezetimibe

Ezetimibe is a selective cholesterol absorption inhibitor, which potently and selectively prevents absorption of cholesterol from dietary and biliary sources by preventing transport of cholesterol through the intestinal wall. This reduces the overall delivery of cholesterol to the liver, thereby promoting the synthesis of LDL receptors and a subsequent reduction in serum LDL-C.Ezetimibe does not affect the absorption of fat-soluble vitamins[2,3]



Structure of Ezetimibe

Mechanism of action

By inhibiting cholesterol absorption at the level of the brush border of the intestine, ezetimibe reduces the amount of lipoprotein cholesterol circulated to the liver. In response to reduced cholesterol delivery, the liver reacts by up regulating LDL-C receptors, which in turn leads to increased clearance of cholesterol from the blood. Ezetimibe is rapidly metabolized in the intestine to its phenolic glucuronide once glucuronidated, it is excreted in the bile, thereby delivering the drug back to the main site of action. Cholesterol absorption studies indicated that the glucuronide appeared more potent than ezetimibe itself, and this is likely because glucuronidated ezetimibe localizes more avidly to the intestine. Ezetimibe and its glucuronide undergo enterohepatic recycling and have a halflife of approximately 24 hours in humans. Ezetimibe and/or the glucuronide metabolite are excreted in the feces (90%) and urine (10%). Pharmacokinetic interaction studies of ezetimibe in humans have found no signifi cant changes in the plasma levels of other medications including statins (atorvastatin, simvastatin, pravastatin, lovastatin, and fl uvastatin), fi brates (gemfi brozil and fenofi brate), digoxin, glipizide, warfarin and oral contraceptives (ethinyl estradiol and levonorgestrel.

COMBINATION THERAPY

Atorvastatin is a selective HMG-CoA reductase inhibitor and causes a decrease in intracellular cholesterol levels and an increased clearance of LDL cholesterol in plasma.

Ezetimibe is a selective cholesterol absorption inhibitor, which potently and selectively prevents absorption of cholesterol through the intestinal wall. Since decrease in LDL receptors and HDL cholesterol is observed in hyperlipidemia,the use of both Atorvastatin and Ezetimibe in combination produces additive effects in hyperlipidemia.

Atorvastatin when used in combination with Ezetimibe causes manifold reduction in LDL cholesterol levels as compared to double the dose of the individual drug when used alone. Moreover, the use of Ezetimibe with Atorvastatin allows for an enhanced effect of the statin at a lower dose and reduction in associated side effects.

Ezetemibe along with statins shows the better impact in the treatment of Atherosclerosis

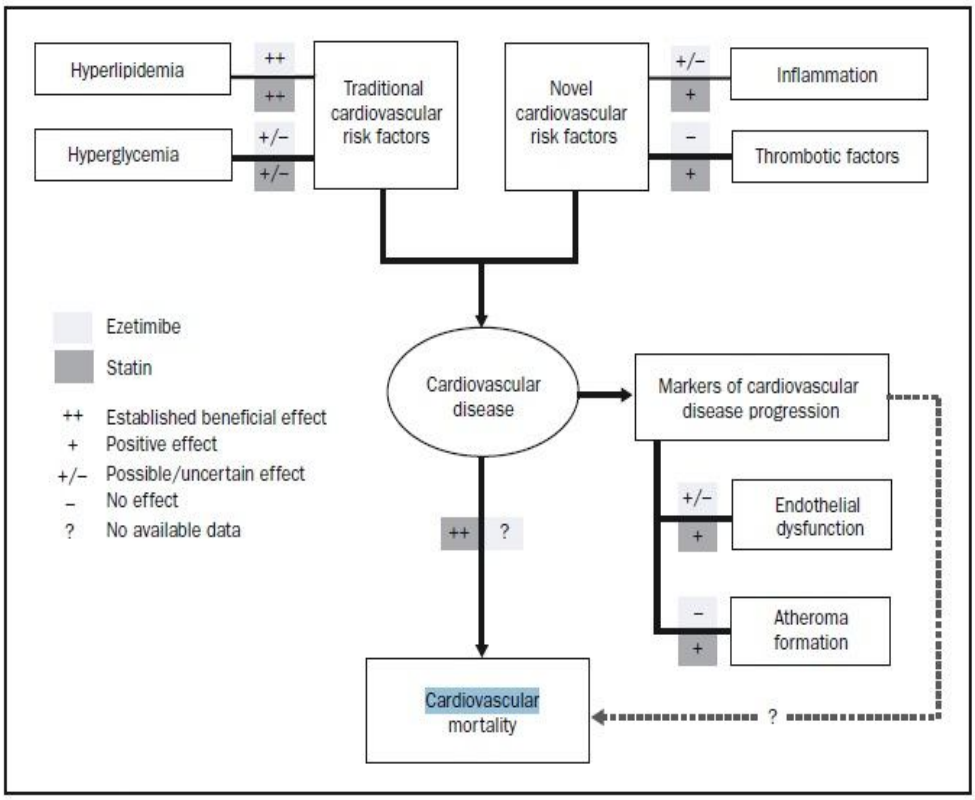


FIGURE. Impact of ezetimibe and statin therapy on various steps in the process of atherosclerosis.

Pharmacokinetics

Atorvastatin

After oral administration, Atorvastatin is rapidly absorbed, with peak serum concentrations reaching within 1 to 2 hours. Extent of absorption increases in proportion to Atorvastatin dose. The absolute bioavailability of Atorvastatin is approximately 14% and the systemic availability of HMG-CoA reductase inhibitory activity is approximately 30%. Mean volume of distribution is approximately 381 liters.

Atorvastatin is ≥ 98% bound to plasma proteins. Atorvastatin is extensively metabolized to ortho- and para hydroxylated derivatives and various beta-oxidation products. Approximately 70% of circulatory inhibitory activity for HMG-CoA reductase is attributed to active metabolites.

Atorvastatin and its metabolites are eliminated primarily in bile following hepatic and/or extra-hepatic metabolism; however the drug does not appear to undergo enterohepatic recirculation. Mean plasma elimination half life of Atorvastatin in humans is approximately 14 hrs, but the half life of inhibitory activity for HMG-CoA reductase is 20-30 hours due to contribution of active metabolites.

Ezetimibe

Ezetimibe is rapidly absorbed and conjugated after oral administration. T_{max} of Ezetimibe and Ezetimibe-glucuronide are 4-12 hrs and 1-2 hrs respectively. Concomitant food administration (high fat or non-fat meals) has no effect on the extent of absorption of Ezetimibe. Ezetimibe can be administered with or without food.

Ezetimibe and Ezetimibe-glucuronide are highly bound (>90%) to human plasma proteins. In humans, Ezetimibe gets rapidly metabolized to Ezetimibe-glucuronide. Ezetimibe and Ezetimibe glucuronide are the major drug-derived compounds detected in plasma, constituting approximately 10-20% and 80-90% of the total drug in plasma, respectively. Both Ezetimibe and Ezetimibe-glucuronide are slowly eliminated from plasma with a half-life of approximately 22

hours for both Ezetimibe and Ezetimibe-glucuronide.
From the pharmacokinetic profile, it is clear that both the drugs are rapidly absorbed after oral administration with their long $t_{1\2}$ for elimination supporting once daily therapy. The T_{max} for Atorvastatin and Ezetimibe glucuronide (pharmacologically active metabolite of Ezetimibe) are also same (i.e. 1-2 hours) which further supports their use in fixed dose combination as a single dose. Further Atorvastatin and Ezetimibe can be administered as a single dose at any time of the day with or without food.

Indications and usage
The FDC is indicated for the treatment of patients with primary hypercholesterolemia.

Contraindications
Patients with known hypersensitivity to Atorvastatin and ezetimibe ,evidence of acute liver disease or unexplained persistent elevations of serum transaminases.

Co – administration of atorvastatin and ezetimibe in general adverse experiences were similar between Ezetimibe administered with HMG-CoA reductase inhibitors and HMG-CoA reductase inhibitors alone. slightly higher in patients receiving Ezetimibe administered with HMG-CoA reductase inhibitor.

CONCLUSION
A gap that will certainly widen with traditional therapy of single inhibition in light recent amendments to the NCEP ATP III guidelines. The new aggressive cholesterol treatment goals call for amore advanced therapeutic approach to maximize the cardiovascular benefits associated with lower LDL-C levels. One logical approach is to target both cholesterol production in the liver and absorption in the intestine. By administering ezetimibe , statin single or ezetimibe co administered with any dose of any statin. We can expect superior LDL-C lowering efficacy and substantially greater proportion to the patients achieving below LDL-C treatment goals. Treating two sources of cholesterol by duel inhibition should be more consider as therapeutic option for all hypercholesterolemia patients whose LDL-C levels are not appropriately controlled approximately 2-3 months after initiating statin monotherapy.

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